

Christine L. Brakel et al.

Serial No. 07/446,235

Filed: December 4, 1989

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### REMARKS

Reconsideration of this application is respectfully requested.

Claims 1-51 are presently pending in this application. Claims 1, 21 and 41 have been amended above. No claims have been added or cancelled by this Amendment. Accordingly, claims 1-51 are presented for further examination.

Minor errors in the specification and the abstract have been corrected for the sake of accuracy and completeness. No new matter has been entered into the disclosure by any of these corrections.

Applicants have amended claims 1, 21 and 41 by deleting the phrase "or unmodified" with respect to the characterization of the N moiety. It is axiomatic under the law that an applicant is entitled to claim less than what is disclosed; accordingly, the foregoing amendments to the claims are proper, particularly in this instance where no broadening of the claims is involved.

Applicants acknowledge with appreciation the indication from the Examiner that all restriction and election requirements have been rescinded, and further that an action on the merits of all the pending claims is presented in the present Office Action.

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**The First Rejection Under 35 U.S.C. §102(b)**

Claims 1-4, 8, 12-14, 19-23, 27-28, 31-33 and 38-51 stand rejected under 35 U.S.C. §102(b) as being anticipated by Miller et al., Biochimie 67:769-776 (1985). In the Office Action (page 2), the Examiner stated that "Miller et al. discloses oligonucleotides possessing methyl-phosphonate linkages that inhibits(sic) the functioning of RNA. Oligomers possessing all or predominately(sic) all methyl-phosphonate groups read on the applicant's broad generic claims using functional language to define the oligomers."

This anticipation rejection is respectfully traversed.

The instant invention is directed to a modified nucleotide compound and to methods of inhibiting the function of an RNA, identifying a nucleotide compound having a combination of nuclease resistance and the ability to form an RNase H substrate when in complex with an RNA, and treating a subject so as to inhibit the function of a target RNA.

Miller et al. disclose oligonucleotide methylphosphonates in which every phosphate bears a methyl group with the exception of perhaps a lone methyl-lacking phosphate at the 5'-end of the oligonucleotide (probably to enhance separation). Unlike the instant invention, this article does not disclose whether RNase H activity would be helpful or even desirable with respect to modified oligonucleotides. In Miller's disclosure, the only reason suggested for the use of the methylphosphonates is to render the oligonucleotides resistant to nucleases, and perhaps secondarily, to form stable complexes with complementary sequences. No mention or suggestion is made in Miller et al. concerning the enhancement of inhibition of RNase expression by catalyzing the breakdown of RNA.

One of the principal thrusts of the instant invention was to construct a modified nucleotide compound that was resistant to nucleases and that was capable of forming an RNase substrate. By designing the modified nucleotide compound to resemble DNA, when hybridized to RNA, the compound could act as a substrate for RNase H. When confronted with a DNA-RNA hybrid, the RNase H cuts off the RNA. When the RNase H is confronted with a DNA-like compound with as many methylphosphonate linkages as provided in Miller's disclosure, no substrate is provided to the enzyme. Thus, in the case of Miller's oligonucleotide methylphosphonates, the enzyme does not recognize any DNA-RNA hybrid that may be formed. Consequently, no substrate for RNase activity is provided, as set forth in the instant invention.

In view of the foregoing explanation, it is believed that a lack of material identity between Miller's disclosed oligonucleotide methylphosphonates and the instantly claimed elements and methods, has been clearly shown. Reconsideration and withdrawal of the anticipation rejection based upon the Miller et al. article is respectfully urged.

#### **The Second Rejection Under 35 U.S.C. §102(b)**

Claims 1-4, 12-14, 19, 21-23, 31-33, 38, 41 and 42-50 stand rejected under 35 U.S.C. §102(b) as being anticipated by Matsukura et al., Proc. Natl. Acad. Sci. (USA) 84:7706-7710 (1987). In the Office Action (page 3), the Examiner stated that "Matsukura et al. discloses oligomers with phosphorothioate modified linkages. These oligomers were resistant to nuclease digestion and were able to inhibit the functioning of RNA."

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This ground of rejection is respectfully traversed.

Applicants respectfully assert that Matsukura et al. cannot be reasonably held to anticipate the instant invention because they provide no evidence or suggestion that their disclosed phosphorothioate oligodeoxyribonucleotides are capable of hybridizing to a target RNA. In fact, Matsukura et al. rely on a different mechanism than target hybridization based on specificity. This is due to the fact that Matsukura et al. are not employing target specific compounds.

In view of the lack of any mention or suggestion in Matsukura et al. concerning the ability to form a DNA-RNA that could serve as a substrate for RNase H, the instant invention must be deemed novel and unobvious over the cited document. Applicants respectfully request, therefore, that the anticipation rejection be withdrawn upon further consideration.

### **The Rejection Under 35 U.S.C. §103**

Claims 1-51 stand rejected under 35 U.S.C. §103 as being unpatentable over Sarin et al., Proc. Natl. Acad. Sci. (USA) 85:7448-7451 (1988) in view of Dash et al., Proc. Natl. Acad. Sci. (USA) 84:7896-7900 (1987). In the Office Action (pages 3 and 4), the Examiner stated:

"Sarin et al. teaches that oligonucleotides possessing methylphosphonate linkages are biologically active and inhibit HIV expression. Furthermore, Sarin et al. teaches that oligomers possessing phosphorothioate,

phosphoramidate, or methylphosphonate linkages all possessed the ability to inhibit HIV.

Dash et al. disclose that complementary antisense oligomers promote the degradation of target mRNA molecules and that this inhibition is irreversible.

Consequently, it would have been obvious to the person of ordinary skill in the art at the time of the invention to make and use antisense oligomers possessing modified linkages known to be resistant to nucleases for the purpose of inhibiting a specific target RNA and further promoting its degradation by RNase(sic) H. The need to optimize both the hybridization of an oligomer to a RNA sequence and its resistance to nucleases is well recognized by the art at the time of the invention."

Applicants respectfully traverse the obviousness rejection on the following basis.

In the case of Sarin et al., they disclose compounds which are exonuclease resistant but not endonuclease resistant. More specifically, Sarin et al. disclose that the inclusion of up to five (5) methylphosphonate linkages in an oligomer of chain length 20 "showed little or no increase in the HIV inhibition capacity." It appears that Sarin et al. did little - if any - investigation into RNase H activity.

On the other hand, Dash et al. provides for oligodeoxynucleotides that can form an RNase H substrate by hybridizing to target mRNA molecules. It is quite clear, however, that Dash's disclosed oligodeoxynucleotides are not subject to degradative enzymes and are not nuclease resistant because the oligodeoxynucleotides are injected into oocytes.

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It is submitted that the two documents, Sarin et al. and Dash et al., do not supplement the teachings which are deficient in the other. As such, the combination of Sarin et al. in view of Dash et al. cannot be reasonably held to render the instant invention obvious. Reconsideration and withdrawal of the obviousness rejection is respectfully urged.

**The Objection/Rejection Under 35 U.S.C. §112, First**  
**Paragraph**

The specification was objected to and claims 1-51 were rejected under 35 U.S.C. §112, first paragraph, for failing to provide an enabling disclosure. In the Office Action (pages 4 and 5), the Examiner stated:

"The specification is not enabling for all M's, N's, and B's defined by the generic claims. The breadth of the claims is so great as to place an undue burden of experimentation upon the person of ordinary skill wanting to make and use the invention. There are hundreds of thousands of possible "modified nucleotides" that fall within the generic claims. However, the specifications(sic) exemplify one the methylphosphonate modification. The disclosure lacks guidance through the thousands of possibilities. While the applicant has provided RNase(sic) and nuclease screening assays, the burden of making and the screening so many is undue. For instance, which modified bases confer endo- or exonuclease resistance at N, M or B?

In addition, the applicant has not documented that ethyl, propyl and butylphosphonates are not so bulky as to interfere with proper hybridization to the RNA and RNase H activity as well. The bulkiness of these larger

alkyl groups creates reasonable doubt that these potential RNA inhibitors will actually work."

The objection and rejection for lack of an enabling disclosure is respectfully traversed.

Applicants note at the outset that each of the instantly claimed elements, M, N and B, are amply defined in the instant specification. In the second paragraph on page 7, N is defined as:

" . . . a phosphodiester-linked unmodified or modified 2'-deoxynucleoside moiety. Preferably, it is an unmodified 2'-deoxynucleotide moiety. When modified, exemplary modified forms include 2,6-diaminopurine, uracil, inosine, 5-halogenated uracil or cytosine, substituted or unsubstituted 7-deazaguanine, 7-deazaadenine, 7-deazinosine, or a methylated adenine, thymine, cytosine or guanine."

Furthermore, M is defined in the subsequent paragraph on page 7 as:

" . . . a moiety that confers endonuclease resistance on the nucleotide component and contains at least one modified or unmodified nucleic acid base. Preferably, it is a C<sub>1</sub>-C<sub>4</sub> alkylphosphonate, such as a methylphosphonate, or is an alpha-phosphodiester linkage. Other examples of M include those selected from the group consisting of an aminophosphonate, phosphotriester, phosphoramidate, carbamate or morpholino-substituted nucleotide. M can also confer exonuclease resistance."

Beginning with the last paragraph on page 7 and continuing through the first three lines on page 8, Applicants define the element B as:

"... a moiety that confers exonuclease resistance to the terminus to which it is attached, preferably directly or indirectly to the deoxyribose moiety of at least one of the 3'- and 5'- terminal nucleotides. Examples of B include an intercalating agent, a methylthiophosphonate, a carbodiimide and an N-hydroxybenzotriazole. B can also be an isourea, a polypeptide or a protein. By way of an additional example, where the modified nucleotide has the formula  $M(N)_x B$ , B can be a modified or unmodified 2', 3'-dideoxyribose nucleotide."

Other descriptions for N, M and B are given in the instant specification, for example, on page 8, fourth and fifth paragraphs.

It is submitted that based upon the original disclosure and the level of skill in the art, a person skilled in the relevant art would have been readily able to make and use the instant invention by selecting - without undue experimentation - appropriate members for each of the elements, N, M and B, defined in the instant claims.

As far as the Examiner's contention concerning the breadth of the claims and the "hundreds of thousands of possible 'modified nucleotides' that fall within the generic claims," Applicants offer the following remarks. Under the law, Applicants are not obliged to exclude in the claim language the inoperative embodiments - if any - for the recited elements, including N, M and B. See, e.g., In re Angstadt, 537 F.2d 574, 190 USPQ 214 (CCPA 1976). In the Angstadt case, the CCPA held that a broad claim to a catalytic process for making hydroperoxides using a broadly defined class of

catalysts was allowable even though the claimed process was unpredictable. In that case, the Court noted:

"Depriving inventors of claims which adequately protect them and limiting them to claims which practically invite appropriation of the invention while avoiding infringement inevitably has the effect of suppressing disclosure. What the dissent seems to be obsessed with is the thought of catalysts which *won't* work to produce the intended result. Appellants have enabled those in the art to see that this is a real possibility, which is commendable frankness in a disclosure. Without undue experimentation or effort or expense the combinations which do not work will readily be discovered and, of course, nobody will use them and the claims do not cover them. The dissent wants appellants to make everything predictable in advance, which is impracticable and unreasonable." [emphasis in original] See 190 USPQ at 219.

As in the Angstadt case, to force Applicants to limit the instant claims to only actual working embodiments and to exclude in the claim language inoperative embodiments of the N, M and B moieties (should there be any in fact), would likewise encourage others to appropriate the instant invention while avoiding infringement. Clearly, such is not the intent of the patent system.

Furthermore, as acknowledged by the Examiner, the instant specification provides RNase and nuclease screening assays (in the examples) for making and screening the various candidates for the N, M and B moieties. Based upon the original disclosure, including the aforementioned screening assays, it is submitted that a person skilled in the art could readily select appropriate members for N, M and B without any undue experimentation. Applicants feel compelled

to point out (again) that under the law, they are not obliged to specifically exclude all of the inoperative embodiments in their invention. In this regard, Applicants would like to draw attention to the 1984 case of Atlas Powder Co. v. E.I. Du Pont De Nemours, 750 F.2d 1569, 1576, 224 USPQ 409, 413-414 (Fed. Cir. 1984). In Atlas Powder, the CAFC stated:

"We agree with the district court's conclusion on enablement. Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude \*\*\* possible inoperative substances \*\*\*\*\*' " [citations deleted, \* in the original]

Applicant also takes careful note that every patent application relies to some extent on the reader's knowledge of the terms, concepts and constructions it embodies and, therefore, relies to some extent upon knowledge of persons skilled in the art to complement that disclosed in order that it be enabling within the meaning of 35 U.S.C. §112. (See, e.g., In re Lange, 644 F.2d 856, 209 USPQ 288 (CCPA 1981)).

The Examiner also raised the point that "the specification exemplify [one modified nucleotide], the methylphosphonate modification." Applicants would like to point out that a broad claim can be enabled by the disclosure of a single embodiment. See, e.g., Cross v. Iizuka, 753 F.2d 1040, 1051, 224 USPQ 739, 748 (Fed. Cir. 1985).

Applicants respectfully assert that the choice of suitable members as N, M and B moieties is well within the ambit of the skilled artisan, given the original disclosure and the level of skill in

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the art. Such an artisan could readily practice the instant invention without any undue experimentation.

Finally, with respect to the sizes of other alkyl substituents (ethyl, propyl and butylphosphonates), Applicants maintain that these groups are not so bulky as to interfere with proper hybridization, in accordance with the instant invention.

In light of the foregoing remarks and established legal principles, Applicants respectfully request that the objection and rejection under 35 U.S.C. §112, first paragraph, be reconsidered and withdrawn.

#### **The Rejection Under 35 U.S.C. §112, Second Paragraph**

Claims 1-51 stand rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. In the Office Action (pages 6-8), the Examiner stated:

[1]"Claims 1 and 21 are so vague, indefinite, and confusing as to be nearly meaningless. The compound of claims 1 and 21 are termed a "modified nucleotide." It is not clear whether this is intended to mean an "oligonucleotide analog" or not. [2]The three generic structures containing M, N and B as variables are confusing. The claims are indefinite because the precise structure and attachment of these moieties to one another is not specified. Is N attached to M or B via the phosphodiester linkage or not? If N is attached to M or B via the phosphodiester linkage, is it through the 3'- or 5'-position? [3]Both M and B are defined functionally instead of structurally. M is any nucleic acid that confers endonuclease resistance on the said "modified

nucleotide." B is any moiety that confers exonuclease resistance to the terminus. Finally, the three generic formulas are vague because there is no indication which end is the 5'- and 3'-terminus.

[4] Claim 3 continues the indefinite functional language by limiting the "modified nucleotide" to those capable of conferring RNase sensitivity to the RNA.

[5] Claim 7 is indefinite because it fails to define specifically the location of the methyl group(s) attached to the bases.

[6] The following two indefinite phrases are used repeatedly throughout the claims: "directly or indirectly attached" and "modified or unmodified." These phrases are vague because they do not specify the particular type of structural modification or attachment that fulfills the functional limitations."

The Examiner stated further that:

[7] "[t]he method claims 21-39 have the same vague and indefinite deficiencies as claims 1-20 but with additional problems. The method of inhibiting RNA is indefinite because it does not specify the concentration of the inhibitor, the method of delivery (added to media or injected into cell, or location of the RNA (either intracellular or isolated).

[8] Claim 40 is indefinite because it fails to specify the criteria for selecting the nucleotide compound having appropriate resistance to nuclease activity. There are no reaction conditions for the nuclease digestions and also no indication concerning the extent of digestion that established that a compound is or is not sufficiently resistant to function as an RNA inhibitor.

[9] Claim 41 is vague for the same reasons that claim 1 and 21 are indefinite. Furthermore, there is no regimen, dosage and schedule, provided for treating a

human or animal. The RNA to be inhibited is not specified either.

[10] Claims 42-50 are even more vague and indefinite than claims 1-20 because of the functional language that is intended to supplant structural definition:

"at least 1 exonuclease and endonuclease resistant component"

"capable of specifically binding with a nucleic acid sequence of interest to inhibit the function thereof"

"when complexed with a complementary RNA, confers RNase H sensitivity upon the RNA"

The rejection for indefiniteness is respectfully traversed.

In view of the rather large number of individual matters which were raised by the Examiner in connection with this rejection, Applicants' undersigned attorney has inserted ten (10) bracketed reference numbers in bold after each above-listed matter in order to make it clear that each and every matter has been thoroughly addressed. The following remarks are directed to the ten reference numbers indicated above.

[1] Applicants respectfully submit that the term "modified nucleotide" is proper usage in the claims, particularly because it is well settled under the law that in formulating his claims, an applicant may use either conventional terms, or he may be his own lexicographer, as long as the meaning of the terms is clear. See, e.g., In re Castaing, 429 F2d 461, 166 USPQ 550 (CCPA 1970). In this instance, Applicants are claiming a "modified nucleotide compound," which term embraces oligo- and polynucleotides suitable inter alia for therapeutic and imaging purposes, including as a delivery vehicle into cells or to cell surfaces. The fact that Applicants are specifically claiming a "modified nucleotide compound" clearly

conveys this meaning, particularly when the claims are read in light of the specification for the purpose of interpreting the meaning of these words. See, e.g., In re Okuzawa, 537 F.2d 563, 190 USPQ 464 (CCPA 1976); and In re Herz, 537 F.2d 549, 190 USPQ 461 (CCPA 1976). Accordingly, the first matter [1] has been satisfactorily addressed.

[2] With respect to the linkage of the N, M and B moieties but without limiting their invention, Applicants point out that these moieties may be linked via the phosphodiester linkages depending on the particular type of moiety that is selected. Furthermore, in the case where these moieties are linked via the phosphodiester linkages, Applicants note that such linkages take the form of the conventionally accepted 5' to 3' format. It is believed that any person skilled in the art would readily recognize this convention in the instant claims. Applicants take careful note that a claim can properly omit information that would be obvious to a person of ordinary skill in the art. See, e.g., In re Skivran, 427 F.2d 804, 166 USPQ 85 (CCPA 1970).

[3] [4] Regarding the purported use of "functional" language, Applicants respectfully assert that the use of such language is not per se objectionable in claims. The issue of "functional" claim language was discussed at length by the Court of Customs and Patent Appeals (the predecessor to the Court of Appeals for the Federal Circuit) in the case of In re Swinehart, 439 F.2d 210, 169 USPQ 226 (CCPA 1971). In that case, the Court approved the use of so-called functional claim language, indicating that:

"[w]e take the characterization 'functional' . . . to indicate nothing more than the fact that an attempt is

being made to define something . . . by what it *does* rather than by what it *is* (as evidenced by specific structure or material, for example). In our view, there is nothing intrinsically wrong with the use of such a technique in drafting patent claims. Indeed we have even recognized in the past the practical *necessity* for the use of functional language." [citation omitted; emphasis in original] [439 F.2d at 212-213]

In this instance, Applicants have properly elected to describe certain elements of their claimed invention using functional terminology. Such language is proper under the statute, particularly where, as in the instant invention, a number of different members are contemplated for the N, M and B moieties.

[5] Concerning the "location of the methyl group(s) attached to the bases" in claim 7, Applicants carefully note that methylated bases are well-known in the art, and that as such, a person skilled in the art would readily comprehend the metes and bounds of this claim. Applicants are prepared to submit evidence in this regard, should the Examiner deem it necessary.

[6] Regarding the use of the phrases "directly or indirectly attached" and "modified or unmodified" in the instant claims, Applicants respectfully point out that the mere use of an alternative expression in a claim is not fatal under the statute even if the alternative expression is not in the format of a recognized exception to the general prohibition against the use of alternative expressions in a claim, namely, Markush expressions. The second paragraph of 35 U.S.C. §112 merely requires that an applicant set out and circumscribe a particular area with a reasonable degree of precision and particularity such that the metes and bounds of the claimed invention are reasonably set forth. See, e.g., Ex parte Head, 214

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USPQ 551 (P.T.O. Bd. App. 1981); In re Moore, 439 F.2d 1232, 169 USPQ 236 (CCPA 1971); In re Swinehart, 439 F.2d 210, 169 USPQ 226 (CCPA 1971); and In re Hammack, 427 F.2d 1378, 166 USPQ 204 (CCPA 1970).

Applicants further point out that §706.03(d) of the MPEP provides in part:

"Generally speaking, the inclusion of (1) negative limitations and (2) alternative expressions, provided that the alternatively expressed elements are basically equivalents for the purpose of the invention, are permitted if no uncertainty or ambiguity with respect to the question of scope or breadth of the claim is presented."

In view of the statutory strictures for definiteness, as set forth above, it is respectfully submitted that the instant claims, especially when viewed in the context of the disclosure, are sufficiently clear in specifying the nature of a direct or indirect attachment between the variously recited elements, or the modification (if any) of such elements. It is further submitted that the phrases in question, "directly or indirectly attached" and "modified or unmodified," are basically equivalents for the purpose of the instant invention. Because the alternatively expressed elements in the claims are basically equivalents for the purpose of the instant invention, the artisan, reading the claims at hand, would not be confused as to what the claims, considered as a whole, would preclude others from doing. See Ex parte Head, *supra*. Moreover, the use of alternative expressions in the instant claims does not present any uncertainty or ambiguity with respect to the question of the scope or breadth of the claims, as set forth in §706.03(d) of the MPEP, *supra*. Accordingly, the use of the aforementioned alternative

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expressions in the instant claims is deemed proper under 35 U.S.C. §112, second paragraph.

In addition, Applicants wish to point out that the U.S. Patent and Trademark Office has issued numerous patents which employ similar alternatively expressed elements in the claims. As one such recent example is U.S. Patent No. 5,082,830 that issued on January 21, 1992 (copy attached as Exhibit A). In fact, most of the thirty-two claims in this patent recite alternatively expressed elements, e.g., "oligo- or polynucleotide," [claims 1-15, 18-21 and 23]; "directly or indirectly attached," [claims 1, 12, 18]; and "biotin or biotin analogue" [claims 2-7, 13 and 20-25].

It is believed that the sixth matter has been overcome by the foregoing remarks and established legal principles.

[7] [8] [9] Issues have been raised in the instant rejection with respect to the following items: lack of a specified inhibitor concentration and method of delivery (claims 21-39); lack of selection criteria for the nucleotide compound having appropriate resistance to nuclease activity and reaction conditions (claim 40); and no treatment regimen, dosage and schedule, no RNA to be inhibited (claim 41). With respect to all of these matters, Applicants offer the following remarks.

Applicants respectfully point out that under the statute, they are not required in this instance to enumerate all of the reaction conditions, concentrations, precise delivery methods, selection criteria, treatment details, and other operative details, under which the instantly claimed methods are carried out, or the claimed compositions are employed. To require Applicants to recite in the claims the litany of conditions and so-called operative details,

which are otherwise routinely known to or readily ascertainable by those skilled in the art, would detract from the key inventive concepts underlying the instant invention. Information concerning any or all of these details is readily available to the skilled artisan, either from the instant specification or from obvious sources of knowledge which could be tapped. Applicants take careful note that a claim can properly omit information that would be obvious to a person of ordinary skill in the art. See, e.g., In re Skivran, 427 F.2d 804, 166 USPQ 85 (CCPA 1970). Furthermore, it is not the role of the claims to enable one skilled in the art to reproduce the invention, but rather to define the legal metes and bounds of the invention. See, e.g., In re Rainer, 305 F.2d 343, 134 USPQ 343 (CCPA 1962); and In re Anderson, 471 F.2d 1237, 176 USPQ 331 (CCPA 1973). Applicants point out that if the claims, read in light of the specification, reasonably apprise those skilled in the art both of the utilization and scope of the invention, and if the language is as precise as the subject matter permits, the courts can demand no more. See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 231 USPQ 81 (CAFC 1986). Based upon the foregoing remarks and above-mentioned legal tests, it is respectfully submitted that the present claims fully satisfy the requirements for definiteness, clarity, conciseness and exactitude under 35 U.S.C. §112.

[10] Applicants maintain that the use of functional language in claim 42-50 is likewise proper usage that does not fail for indefiniteness under the statute. In this regard, Applicants reiterate their remarks which were presented in connection with matters [3] and [4] (see this Amendment, page 16, second full paragraph, through the middle of page 17), and respectfully urge that a person skilled in the art would readily comprehend the metes and

bounds of the instant invention as defined in part by the functional language contained in the claims.

In view of the foregoing amendments and remarks, Applicants respectfully assert that all of the grounds for objection and rejection in this case have been overcome in toto. It is submitted, therefore, that the instant claims, 1-51, are in condition for allowance, and they respectfully seek an early indication to that effect.

#### **Submission of Art-Related Documents**

In order to comply with their duty of disclosure, Applicants are filing concurrently, with this Amendment, a Supplementary Information Disclosure Statement Under 37 C.F.R. §§1.56 and 1.99.\* In the Supplementary Statement, Applicants are providing a copy of each of the following four (4) documents as well as a completed Form PTO-1449:

1. PCT International Publication No. WO 90/08838, published on August 9, 1990 [Exhibit 1];

2. PCT International Publication No. WO 89/05358, published on June 15, 1989 [Exhibit 2];

\* A previous Information Disclosure Statement was filed concurrently with Applicants' May 31, 1991 Request for Reconsideration of Restriction Requirement Under 37 C.F.R. §1.143. The four (4) documents submitted in the Supplementary Statement came to the attention of Applicants' undersigned attorney from the European search report that was issued in connection with the corresponding European application, Eur. Pat. Appl. No. 90 12 3109.2, published as EP 0 431 523 on June 12, 1991.

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3. PCT International Publication No. WO 89/08146,  
published on September 5, 1989 [Exhibit 3]; and

4. Quartin et al., "Number and distribution of  
methylphosphonate linkages in oligodeoxynucleotides affect exo-  
and endonuclease sensitivity and ability to form RNase II  
substrates," Nucleic Acids Research 17:7253-7262 (1989) [Exhibit  
4].\*

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### SUMMARY AND CONCLUSIONS

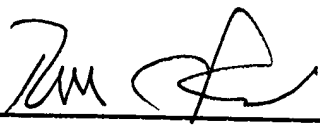
Claims 1-51 are presented for further examination. Claims 1, 21 and 41 have been amended; no claims have been added or cancelled by this Amendment. Furthermore, no new matter has been inserted by any of the foregoing changes to the instant claims or specification.

This Amendment is accompanied by and includes a Request For a Three Month Extension of Time. The Patent and Trademark Office is hereby authorized to charge Deposit Account No. 05-1135 for the requisite fee of \$810.00, as set forth in 37 C.F.R. §1.17(c). In addition, an Information Disclosure Statement Under 37 C.F.R. §§1.56 and 1.99 (including Exhibits 1-5) is being concurrently filed with this Amendment. The Patent and Trademark Office is further authorized to charge Deposit Account 05-1135 for any other fees in connection with this Amendment and to credit any overpayment thereto.

In view of the above discussion of the issues, Applicants respectfully submit that each of claims 1-51 is in condition for allowance. A favorable and speedy reconsideration of their rejection is requested. If any of these claims are found not to be in condition for allowance for any reason, the Examiner is respectfully requested to telephone the undersigned at (212) 924-5409 or 924-9578 to discuss the subject application.

Respectfully submitted,

FEBRUARY 26, 1992  
Date

  
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